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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,537	09/09/2000	Adrienne W. Paton	19957-014500US	3288

20350 7590 07/03/2002

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/658,537	Applicant(s) PATON ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-116* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15,25,36,37,41,43,45-70,73-85,88-91,94,97-107 and 110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims withdrawn from consideration are 10-14,16-24,26-35,38-40,42,44,71,72,86,87,92,93,95,96,108,109 and 111-116.

DETAILED ACTION

Non-Final Rejection

Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 are pending examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Australia on 9/10/99. It is noted, however, that applicant has not filed a certified copy of the Australian application as required by 35 U.S.C. 119(b).

Drawings

Applicants are required to submit drawing corrections or proposed corrections with the response to this office action or the response will be considered non-responsive. See 37 CFR 1.85(a).

Information Disclosure Statement

The information disclosure statement filed 9/13/01 paper no. 6 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted that the IDS list several US Patents, however, the US Patents are not included with the other references listed on the IDS. Therefore, only the other articles will be considered and the US Patents will not be considered. Applicants should supply the US patents listed on the IDS, if they want the examiner to consider and initial the US patents on the 1449.

Response to traversal of the Election/Restriction

Applicants elect Group I and species with traverse because the claimed invention by applicants arises out of the common inventive concept or idea; search the claims as filed would place no undue burden on the Examiner; Applicants wish to remind the examiner that when compositions claims are allowed, under MPEP 821.04, method claims must be rejoined. See pages 1-3.

Applicants' traversal is acknowledged and is not found persuasive because the restriction set forth in paper no. 7 displays that Groups I-III are distinct. In addition, the literature search for Group I is not required for Groups II and III. Furthermore, the classification of each Group into a different class requires a separate search status on the basis of the classification system, which recites an enormous number of potential and patentably distinct inventions within each class and subclass. In conclusion, each of the inventions I-III comprise materially distinct steps, and/or generate different functions and effects, and thus, are not required for use with one another. Therefore the elected invention group I is distinct from groups II and III.

Therefore, the restriction is deemed proper and is made **Final.**

However, claims 86-87, 108-109, and 111-116 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions and the non-elected species in claims 10-14, 16-24, 26-35, 37-40, 42, 44, 71, 73, and 91-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the word "means". Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 58, 61, 65-67, 74-75, 83, 98, 105, 107, and 110 are objected to because of the following informalities:

Claim 58, a comma should be inserted before the conjunction term "and".

Claim 61, a comma should be inserted before the conjunction term "or".

Misspelling of the words "stabilize" in claim 65 and "synthesizing" in claims 66 and 74.

Claims 67 and 110 are objected to because of the term "including". In view of compact prosecution, the term "including" will be read as comprising.

Remove the comma after the chemical agent formalin in claim 107.

Claim 75 is objected to for reciting grammatically improper phase, "wherein genes encoding **the** all or some of the one or more glycosyl transferase are modified to prevent phase variation."

Claims 83 and 105, a comma should be inserted before the conjunction term "and".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 as best understood, are readable on a genus of a recombinant microorganism that displays on its surface a binding moiety that competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism, wherein the genus of the recombinant microorganism is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 60-63, 67, 78-80, 78, 88, 99, 100-102 as best understood, are readable on a genus of a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of

colicins, wherein the genus of the recombinant microorganism is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 64-65, as best understood, are readable on a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation, wherein the genus of the recombinant microorganism is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a recombinant microorganism that displays on its surface a binding moiety that competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism. Furthermore, the specification contemplates that the acceptor moiety is endogenous to the microorganism and the glycosyltransferase is encoded by an exogenous nucleic acid. In addition, the specification

contemplates a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins. The disclosure further contemplates a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation. The as-filed specification provides sufficient description of glycosyl structures of receptors for toxins (pages 27-28) and states that, "many glycosyltransferase are known, as are their polynucleotide sequences" (pages 10-18). The disclosure further teaches that the acceptor moiety can consist of lipids or oligosaccharides on the outer surface of the microorganism (page 59). However, the as-filed specification and the art of record only provide sufficient description for sub-species (E.Coli) of a recombinant microorganism.

Therefore, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of acceptor moieties and/or a genus of a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins and/or a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are

naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of acceptor moieties and/or a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins and/or a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins and/or a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of

applicant's effective filing date. Claiming an unspecified a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation and/or acceptor moieties and/or a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation and/or acceptor moieties and/or a recombinant microorganism, wherein the microorganism has reduced production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the

receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-9, 15, 25, 36-37, 41, 43, 45-70, 73-85, 88-91, 94, 97-107, and 110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A recombinant bacterium comprising an exogenous nucleic acid encoding a glycosyltransferase that produces a specific sugar moiety, which is a mimic of a sugar moiety from a specific bacteriological toxin, when expressed on the cell surface attached to a surface-expressed acceptor molecule of the recombinant bacterium, wherein the recombinant bacterium is Escherichia coli (E.coli), and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a recombinant microorganism wherein all or some of the one or more glycosyl transferase are naturally occurring and/or wherein genes encoding all or some of the one or more glycosyl transferase are modified to stabilize phase variation and/or acceptor moieties and/or a recombinant microorganism, wherein the microorganism has reduced

production of external masking polysaccharide molecules other than said acceptor molecule to enhance exposure of the receptor mimic and/or is selected to provide some resistance to anti-microbial activity of micro-flora potentially resident in the gut and/or is resistant to the major families of colicins), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. used for producing a mimic of a receptor for a toxin on the cell surface of a recombinant microorganism using an acceptor moiety to transport the receptor to the outer surface.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is in the field of producing a recombinant microorganism comprising an exogenous nucleic acid encoding a glycosyltransferase that produces a receptor for a toxin and expressing the receptor on the surface of the microorganism. The field of the invention lies in genetically modifying a microorganism to express an exogenous nucleic acid encoding a glycosyltransferase that is operably linked to an acceptor moiety that is expressed on the outer surface of the microorganism.

A brief description of the examples (pages 41-66) provided by the as-filed specification follow: Example 1 is the construction of a harmless recombinant bacterium capable of incorporating the trisaccharide Galalpha[1-4]GalB[1-4]Glc into the outer core region of the its lipopolysaccharide, wherein the trisaccharide is capable of binding several types of Shiga toxin. Furthermore, the example encompasses testing the recombinant bacterium to protect mice from fatal infection with STEC. Example 2 examined the capacity of oral administration of killed

recombinant cells to protect mice from otherwise fatal challenge of STEC. Example 3 is the construction of a recombinant bacterium expressing globotetraose on its surface and examined its capacity to bind and neutralize STX2e in vitro. Example 4 teaches that C.difficle exotoxin A binds to several human glycolipids, all of which contain Galbeta[1-4]GlcNAc moiety and genes encoding transferase capable of assembling this epitope are also found in Neisseria IgT locus. Example 4 further teaches the production of this epitope on recombinant bacterium and asserts that the capacity to bind and neutralize exotoxin A can be assessed using a standard protocol. The example further points out that in vitro studies indicate that even stronger binding occurs between exotoxin A and the trisaccharide Galalpha[1-3]Galbeta[1-4]GlcNAc-, even though it is not present in humans, see Karlsson, 1998, Mol. Microbiology. Therefore, a strain expressing this epitope can be constructed by incorporation a gene encoding a transferase capable of forming the necessary epitope and a database search for a source of such a transferase. Example 5 contemplates the production of Gm1, which is a mimicked by the LPS outer core of several Camplyobacter jejuni strains and using the sequence data the appropriate genes can be identified for assembly of the Gm1 mimic. Examples 6-8 contemplate extrapolate from the model systems discussed above to block bacterial adhesion. Example 9 is the production of detection method using the recombinant microorganism constructed or contemplated by the above examples.

In view of the breadth of the claims, the working examples, the guidance provided by the as-filed specification; and the art of record, the claimed invention provides sufficient guidance for one skilled in the art to make and/or use a recombinant bacterium, wherein the bacterium is an E.coli, comprising and exogenous nucleic acid encoding a glycosyltransferase operably linked to a gene encoding an endogenous lipopolysaccharide that is expressed on the surface of the

microorganism, wherein the expression of the exogenous nucleic acid results in a mimic of a receptor for a toxin of a pathogenic microorganism. However, the claimed invention is not enabled for the full scope of the clamed invention because the as-filed specification fails to provide sufficient guidance for one skilled in the art to use a recombinant microorganism that displays on its surface a binding moiety that, when administered to an animal, competes with a ligand for binding to a receptor for the ligand, wherein the binding moiety comprises an oligosaccharide which comprises a sugar residue that is attached to an acceptor moiety by a glycosyltransferase that is encoded by an exogenous nucleic acid which is present in the microorganism for the following reasons:

First, with respect to the claimed invention comprising the making and/or using of a genus of recombinant microorganism, the disclosure only provides sufficient guidance for one skilled in the art to make and/or use the bacterium, E.coli; because the as-filed specification fails to provide sufficient guidance for one skilled in the art to make and/or use an essential feature of the microorganism that is attaching a binding moiety (e.g. sugar residue, that is a mimic of a receptor on a pathogenic microorganism) to an acceptor moiety (e.g. lipopolysaccharide (LPS) that is transported to the exterior cell surface of the microorganism). This essential feature is required for one skilled in the art to practice the claimed invention because the binding moiety is used to compete with a ligand (e.g. receptor for a toxin) that binds to an endogenous receptor in an animal to reduce the level of that particular toxin in the animal. The state of the art teaches linking a Shiga toxigenic receptor (Stx2) to a mutated LPS in an E.coli to produce a recombinant E.coli and using the recombinant microorganism to protect mice from challenge with an otherwise 100% fatal dose of Shige toxigenic E.coli (Paton et al. Nature Medicine, Vol. 6, pp.

265-270, 2000). Furthermore, Paton teaches that, "many bacterial and viral pathogens exploit oligosaccharide moieties of glycoproteins or glycolipids on the surface of eukaryotic cells as receptors for toxins, adhesions, or other ligands. Construction of a given mimic requires the identification of the specific glycosyltransferase required for synthesis, and insertion of gene encoding these into a heterologous host producing appropriate surface-expressed acceptor molecule" (pages 267-268). E.coli is a species of the genus, Gram-negative bacteria, which have a LPS, which is an essential component of bacterial cell surface of this genus. In addition, there is also another genus of bacteria, which is labeled, Gram-positive, which do not have a LPS as part of the bacterial cell surface. Finally, there is Mycoplasma, which is a group of bacteria that lack a cell wall. The art of record is absent about using the surface-expressed LPS from E.coli as an accepted model for reasonably extrapolating to the genus of surface-expressed acceptor molecule in a genus of microorganism comprising yeast, fungi, LPS-surface expressed acceptor molecule in other gram-negative bacteria, or any other type of bacteria (e.g. Mycoplasma or gram-positive bacteria). Therefore, in view of the unpredictability of the identifying a representative number of microorganism with a surface-expressed acceptor molecule that can be used for attaching an binding moiety to and expressing the cell's surface, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from using a recombinant E.coli to the full breadth of the claimed invention.

In addition, with respect to the claimed invention encompassing making and/or using any binding moiety that when administered to an animal competed with a ligand for binding to a receptor for the ligand, the as-filed specification only provides sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a sugar moiety and/or sugar moiety in the

presence of suitable sugars because the genus of binding moiety is not sufficiently described in the as-filed specification. For example, the art of record teaches that many bacterial and viral pathogens exploit oligosaccharide moieties of glycoproteins or glycolipids on the surface of eukaryotic cells as receptors for toxins, adhesions, or other ligands. Thus, it is not apparent how one skilled in the art would be able to reasonably extrapolate from making and/or using sugar moieties to any binding moieties, including glycolipids and glycoproteins because of the complex nature of these receptors and the requirement for the correct three dimensional structure of these moieties and the correct expression of these moieties on the surface of a recombinant bacterium in order to successfully compete with a ligand for binding to a receptor for that ligand. In addition, the as-filed specification lacks sufficient guidance for the source for producing these moieties (glycoproteins and glycolipids) in a recombinant bacterium. Therefore, in view of the art of record and the lack of guidance provided by the as-filed specification, the claimed invention is only enabled for making and/or using sugar moieties.

Furthermore, if the applicant is able to overcome the concerns set forth above for making and/or using a surface expressed acceptor molecule from a representative number of microorganisms, there are concerns provided by the state of the art for expressing an exogenous nucleic acid encoding a glycosyltransferase operably linked to an appropriate surface-expressed acceptor molecule in a representative number of microorganisms. At the time the invention was filed, the as-filed specification provides sufficient guidance for expressing an exogenous nucleic acid in E.coli and one skilled in the art would have been enabled to make and/or use species of microorganisms (yeast, fungi) to express an exogenous nucleic acid encoding a glycosyltransferase in a culture and isolating exogenous nucleic acid from the culture. However,

at the time application was filed and in view of the breadth of the claimed invention (recombinant microorganism), the as-filed specification fails to provide sufficient guidance for one skilled in the art to make and/or use a representative number of species for one skilled in the art to practice the full scope of the claimed invention because the disclosure does not provide sufficient guidance for what microorganisms are/are not considered enabled for one skilled in the art to make and/or use, which would require an undue amount of experimentation for one skilled in the art to reasonably extrapolate from the working examples using E.coli in the as-filed specification to a genus of microorganisms. For example, the state of the art teaches that replication of plasmid DNA in gram-negative bacteria is dependent on three stages; initiation, elongation, and termination. The first stage, initiation depends on plasmid-encoded properties such as the replication origin (oriC) and in most cases, the replication initiation protein (Rep protein). Most plasmid studies exhibit a narrow host range limited to E.coli and related bacteria (Kues et al., Replication of plasmids in gram-negative bacteria, Micriobiol Rev., Vol. 53, 1989, (abstract) Medline [online], Bethesda, MD USA: United States National Library of Medicine [retrieved on 6/26/02], Medline accession number 2687680). The art of record also teaches that several species of oriC have been isolated (Moriya et al., Plasmid, Vol. 41, pp. 17-29, 1999). Moriya teaches that:

> Studies in E.coli have taken the lead in research of initiation mechanism of the bacterial chromosome replication and have provided considerable insight into this key regulation mechanism which is thought to be basically common in eubacteria. However, the picture is far from clear. In Bacillus Subtilis, our studies suggest that the mechanism that determines the time of initiation of chromosome replication is different from E.coli (page

17). Further analysis of initiation of replication using new technology will help elucidate the key mechanisms controlling bacterial cell cycle (page 26).

In view of the art of record and the lack of guidance provided by the as-filed specification for the making and/or using the genus of microorganism (e.g. bacteria), the as-filed specification only provides sufficient guidance for one skilled in the art to make and/or use E.coli in the claimed invention because of the reasons set forth above. Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of bacteria (E.coli) to the full scope of the claimed invention that would display a binding moiety that competes with a ligand for binding a receptor for the ligand. In addition, it is not apparent how expressing a sugar moiety in a simple prokaryote, like E.coli, can be reasonably extrapolated to expression of the same sugar moiety in eukaryotic microorganisms because of the different pathways in the more complex eukaryotic microorganisms. More specifically, one skilled in the art understands the difference of gene expression in prokaryotes versus eukaryotic organism. Take post-translational processing for example, in prokaryotes, most mRNA transcripts function in translation without further modification, however, in eukaryotes, mRNA is produced in the cell nucleus while translation occurs in the cytosol and eukaryotic mRNA transcripts can undergo post-translation processing while still in the nucleus. Even if a protective response has been shown in mice using the exemplified mice, it is not apparent as to how the mouse model using the recombinant E.coli is reasonably extrapolated to the full scope of the claimed invention, encompassing using any microorganism particularly given that there is no evidence showing that the recombinant E.coli is a general phenomenon, and given the doubts expressed in the art of record.

In addition, with respect to claims encompassing making and/or using a microorganism that is endogenously resistant to the major families of colicins in claims 63, 80, and 102, the as-filed contemplates using a genus of microorganisms listed above and in view of the state of the art only provide sufficient guidance for one skilled in the art to make and/or use E.coli because the as-filed specification only asserts that one skilled in the art can make and/or use a genus of either microorganism. One skilled in the art would know that a colicin is considered to be an antibacterial substances that are produced by strains of intestinal bacteria (as of *E. coli*) having a specific plasmid and that often act to inhibit macromolecular synthesis in related strains. To support the unpredictability of what microorganism endogenously produce colicin, Brackelsberg et al. (Vet. Res. Commun., Vol. 21, abstract, 1997, Medline [online], Bethesda, MD USA: United States National Library of Medicine [retrieved on 6/28/02], Medline accession number 9266660) teaches that eight salmonella tymphimurium and eight salmonella dublin were isolated from cattle and none of the isolates produced colicin. Thus, in view of the state of the art, the disclosure does not provide sufficient guidance and/or factual evidence for what microorganisms are resistant to the major families of colicins other than E.coli. In view of the lack of guidance provided by the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a plasmid in E.coli that is resistant to colicin to making and/or using a genus of microorganisms (gram-positive bacteria, Mycoplasma, yeast fungi, etc.) that are endogenously resistant to colicins.

In addition, with respect to claims encompassing making and/or using a genus of genes encoding all or some of the one or more glycosyl transferases are modified to prevent or stabilize phase variation in claims 65 and 75. Other than asserting that genes encoding all or some of the

one or more glycosyltransferases can be modified to prevent phase variation, the as-filed specification is absent of any examples for one skilled in the art to reasonably extrapolate from the assertion to making and/or using a representative number genes to practice the genus of genes encoding all or some of the one of the glycosyltransferase are modifies to prevent phase variation. One skilled in the art understands that phase variation is the switching of chemical structure (e.g. terminal LPS structure on a cell's exterior surface) and that the breadth of the claims read on an enormous number of chemical structures (LPS). For example, the state of the art teaches lipo-oligosaccharide (LOS) biosynthesis loci from 11 Campylobacter jejuni strains expressing a total of 8 different ganglioside mimics in their LOS outer cores (Gilbert et al., JBC, Vol. 277, abstract, 2002). Gilbert further teaches that, "many pathogenic bacteria have variable cell-surface glycoconjugates...This variation is caused by the diversity of monosaccharide components and the linkage between them...The variation of these glycan structures can sometimes be correlated with a specific gene complement, but it is probable that other genetic mechanisms are also employed to create variable cell-surface glycoconjugates (page 327). Therefore, in view of the lack of guidance provided by the as-filed specification for what amino acids are considered essential to stabilize or prevent phase variation, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion to the full scope of the making and/or using genes encoding glcosyltransferases that can be modified to prevent or stabilize phase variation.

Furthermore, with respect a method of administering a recombinant bacterium to a mammal to reduce adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal, the as-filed specification fails to provide sufficient guidance for how

controlled experiments using mice reasonably correlate to reducing adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal because the state of the art teaches that commencement of therapy immediately after challenge was 100% protective, but in a mammal setting such early intervention will be possible only for contacts of patients with confirmed cases, who have not yet, or have only just, become infected with a pathogenic microorganism, STEC (Paton et al., Infection and Immunity, Vol. 69, pp. 1389-1393, 2001). Thus, it is not apparent to one skilled in the art how to use the recombinant bacterium in any method sought forth in the claimed invention because of the unpredictability of determining when a mammal has, does not yet have or have only just become infected with a microorganism and if at later time points in the infection the recombinant microorganism can reduce the amount of toxin in the mammal. Therefore, it would take an undue amount of experimentation for one skilled in the art to reasonably extrapolate from controlled experiments to any method of reducing adherence of a pathogen or a toxin produced by the pathogen in the mucosal surface of the mammal.

Furthermore, with respect to a mimic of a receptor for a toxin in claims 1, 7, 68, 69, 88, and 90, the as-filed specification and the art of record only provide sufficient guidance for a toxin produced by bacteria because it is not apparent what other microorganisms (yeast, virus, fungi) produce toxins other than bacteria. Also, one skilled in the art would reasonably determine in view of the breadth of the claim that a toxin could be a chemical toxin and the as-filed specification lacks any description or factual evidence for any type of chemical toxin (e.g. radioactive material, carcinogens, etc.). Therefore, the as-file specification is only enabled for making and/or using a mimic of a receptor for a bacteria toxin.

Thus, in view of the In re Wands' Factors, the disclosure is only enabled for 1 listed above and is not enabled for the full scope of the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material, the lack of direction or sufficient guidance provided by the as-filed specification for the production of a representative number of recombinant microorganism to practice the claimed invention. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of a genus of recombinant microorganism, in particular when the expression of a binding moiety attached to an acceptor moiety can compete with a toxin, the unpredictable state of the art with respect to the expressing an oligosaccharide attached to a LPS that is expressed on the cell's exterior surface, and the breadth of the claims drawn to any recombinant microorganism, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 36, 52-53, 60, 62-65, 73-75, 79-80, 84, 89-90, 97-107, and 110, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 36 are objected to under MPEP 2173.05(h), as using improper Markush group language. The claim recites "goats, rabbits, sheep, geese, ducks." The terminology "**and**" or "**or**" is acceptable Markush group language. The term "and" should inserted before the last species in the Markush Group.

Claims 1, 52, 53, 60 recite the limitation "the receptor mimic". There is insufficient antecedent basis for this limitation in the claim. There could be many compositions that could be a receptor mimic and the disclosure does not distinctly point out and claim which receptor mimic.

Note: The independent claim (claim 1) is rejected with claims 52-53), because when claim 1 is read a whole, claims 52-53 are encompassed by the breadth of the independent claim.

Claim 52 recites the limitation "the exogenous transferases" in line 3, page 75. There is insufficient antecedent basis for this limitation in the claim.

Claim 62 recites the limitation "the gut" on line 3 on page 76. There is insufficient antecedent basis for this limitation in the claim.

Claims 79 and 101 recites the limitation "the gut". There is insufficient antecedent basis for this limitation in the claim.

Claim 63 recites the limitation "the major families of colicins" in line 2, page 76. There is insufficient antecedent basis for this limitation in the claim.

Claims 80 and 102 recite the limitation "the major families of colicins". There is insufficient antecedent basis for this limitation in the claim.

The term "wherein all or some of the one or more glycosyl transferases are naturally occurring" in claims 64 is a relative term which renders the claim indefinite. The term "wherein all or some" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term because it does not define under what conditions when "all" or "some" is preferred.

The term "wherein all or some of the one or more glycosyl transferases" in claims 65 and 75 is a relative term which renders the claim indefinite. The term "wherein all or some" is not defined by either claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term because it does not define under what conditions when "all" or "some" is preferred.

Claims 73, 74, and 97 recite the limitation "said organism". There is insufficient antecedent basis for this limitation in the claim. There are many organisms known to one skilled in the art and the disclosure does not distinctly point out and claim which organism.

Note: The independent claim (claim 73) is rejected with claim 74, because when claim 73 is read a whole, the breadth of the independent claim encompasses claim 74.

The statement in claims 89-90, 97-107, and 110, "... **a** receptor mimic as in claim" is indefinite because it does not point out which receptor; **a** receptor is referring to in each claim. The dependent claims should state "The method.... the receptor mimic as in claim."

Claims 84 and 106 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: how the microorganism being killed is positively linked to the pre-amble "A method of administering" of the independent claim. Clarification is requested.

Claim Rejections - 35 USC § 102

The following 102(a) rejection applies to the scope of enablement and because as noted above, the applicants did not provide a certify copy of the Australian application filed on 9/10/99.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8, 25, 46, 51, 53, 55-59, 63, 66-69, 74, 76, 78-80, 82-85, 88-90, 97-99, 102, and 104-107 are rejected under 35 U.S.C. 102(a) as being anticipated by Paton et al. (Nature Medicine, Vol. 6, March 2000, pages 265-270). Paton teaches a recombinant bacterium (E.coli) that displayed a Shigan toxin receptor mimic on its surface and it absorbed and neutralized Shiga toxin with very high efficiency in mice (abstract, Figure 1, page 265, and page 266). Paton further teaches that formaldehyde-killed E.coli could be used in the method (page 269).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 15, 25, 37, 41, 43, 46, 51-52, 55-59, 63, 66-70, 73-74, 76, 78, 80, 82-85, 88-91, 94, 98-99, 102, and 104-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paton et al. (Nature Medicine, Vol. 6, March 2000, pages 265-270) taken with applicants' own admission that any receptor mimic of a toxin can be selected from any one of the receptors set out in Table 1 (pages 27-28, lines 1-5). Paton teaches a recombinant bacterium (E.coli) that displayed a Shigan toxin receptor mimic on its surface and it absorbed and neutralized Shiga toxin with very high efficiency in mice (abstract, Figure 1, page 265, and page 266). Paton further teaches that formaldehyde-killed E.coli could be used in the method (page 269). However, Paton does not specifically teach a recombinant bacterium (E.Coli) comprising a mimic of a receptor for a cholera toxin and using the oligosaccharide Galbeta[1-3]GalNAcBeta[1-4]Galbeta[1-4]Glc, NeuNAcalpha[2-3].

However, at the time the invention was made, Paton teaches that the production of a recombinant bacterium expressing a receptor mimic for Shiga toxigenic is a prototype for a new 'probiotic' strategy for the treatment of a wide range of enteric disease. Paton further teaches that many bacterial pathogens exploit oligosaccharide moieties of glycoproteins or glycolipids on the surface of eukaryotic cells as receptors for toxins (pages 267-268). In addition, applicants' own admission that the receptor for cholera toxin and the oligosaccharide, Galbeta[1-3]GalNAcBeta[1-4]Galbeta[1-4]Glc, NeuNAcalpha[2-3], were well known (pages 27-28).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Paton in further view of applicants' own admission, namely to produce a recombinant E.coli comprising a mimic of a receptor for a cholera toxin and the oligosaccharide Galbeta[1-3]GalNAcBeta[1-4]Galbeta[1-4]Glc, NeuNAcalpha[2-3]. One of ordinary skill in the art would have been motivated to combine the teaching because the recombinant E.coli was well known to one of ordinary skill in the art and applicants' admission that a receptor mimic for cholera toxin and oligosaccharide Galbeta[1-3]GalNAcBeta[1-4]Galbeta[1-4]Glc, NeuNAcalpha[2-3] can be used to produce the cholera toxin expressing recombinant E.coli.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
7/1/02

DAVE T. NGUYEN
PRIMARY EXAMINER